US006541116B2

(12) **United States Patent**
Michal et al.

(10) **Patent No.: US 6,541,116 B2**
(45) **Date of Patent: Apr. 1, 2003**

(54) **SUPEROXIDE DISMUTASE OR SUPEROXIDE DISMUTASE MIMIC COATING FOR AN INTRACORPOREAL MEDICAL DEVICE**

(75) Inventors: **Eugene T. Michal**, San Francisco, CA (US); **Christopher J. Buchko**, Redwood City, CA (US); **Deborah L. Kilpatrick**, Mountain View, CA (US); **Stephen J. Bigus**, San Jose, CA (US)

(73) Assignee: **Advanced Cardiovascular Systems, Inc.**, Santa Clara, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 83 days.

(21) Appl. No.: **09/827,977**

(22) Filed: **Apr. 6, 2001**

(65) **Prior Publication Data**

US 2002/0009535 A1 Jan. 24, 2002

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/240,914, filed on Jan. 29, 1999, now Pat. No. 6,287,285, which is a continuation-in-part of application No. 09/016,694, filed on Jan. 30, 1998, now Pat. No. 6,221,425.

(51) **Int. Cl.**[7] **B32B 7/04**

(52) **U.S. Cl.** **428/420**; 428/425.9; 428/473.5; 428/413; 428/500; 428/524; 623/1.11; 623/1.44; 623/1.46; 623/1.49; 623/1.39; 623/926; 623/23.64; 623/23.7; 604/507; 604/508

(58) **Field of Search** 428/420, 425.9, 428/473.5, 413, 500, 524; 623/1.44, 1.11, 1.46, 1.49, 1.39, 926, 23.64, 23.7, 2.42; 604/507, 508

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,824,049 A * 10/1998 Ragheb et al. 623/1.44
5,874,421 A 2/1999 Riley et al. 514/161

OTHER PUBLICATIONS

Salvemini et al. "A Nonpeptidyl Mimic of Superoxide Dismutase with Therapeutic Activity in Rats" Science, 286:304–306, (1999).

Udipi et al. "Modification of Inflammatory Response to Implanted Biomedical Materials in vivo by Surface Boun Superoxide Dismutase Mimics", J. Biomed. Mater. Res., 51(4):549–560, (2000).

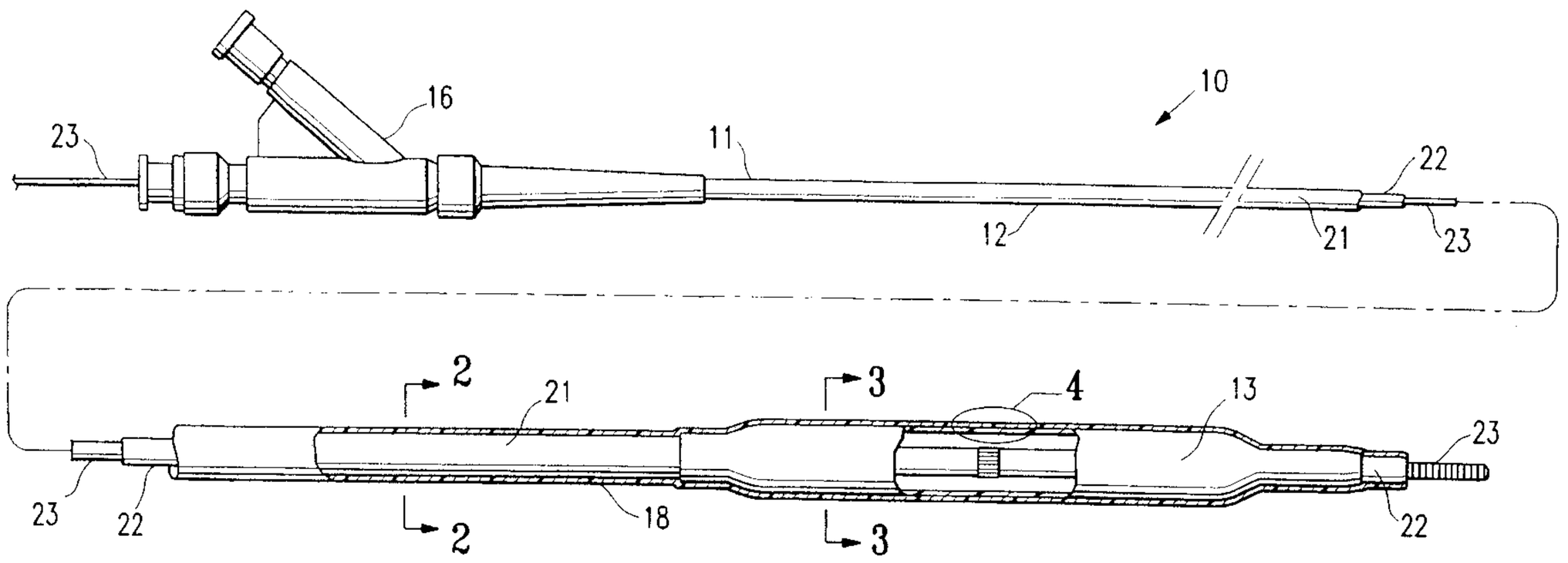
* cited by examiner

Primary Examiner—James J. Seidleck
Assistant Examiner—Melanie Bissett
(74) *Attorney, Agent, or Firm*—Filwider Patton Lee & Utecht, LLP

(57) **ABSTRACT**

A method of providing a therapeutic, diagnostic or lubricious hydrophilic coating on an intracorporeal medical device and the coated device produced thereby, wherein the coating is durable. In one embodiment, the coating comprises a polymerized base coat and a top coat having a therapeutic, diagnostic or hydrophilic agent, where the base coat has a binding component which binds to the top coat, and a grafting component which binds to the binding component and adheres to the device. In another embodiment, the coating comprises a blend of an agent, a grafting component, and salt. In one embodiment, the therapeutic agent is superoxide dismutase or a superoxide dismutase mimic. The coating of the invention may be applied to a medical device with a polymeric surface such as a polymeric catheter, or a metal device such as a stent coated with a polymeric primer or without a primer.

23 Claims, 4 Drawing Sheets



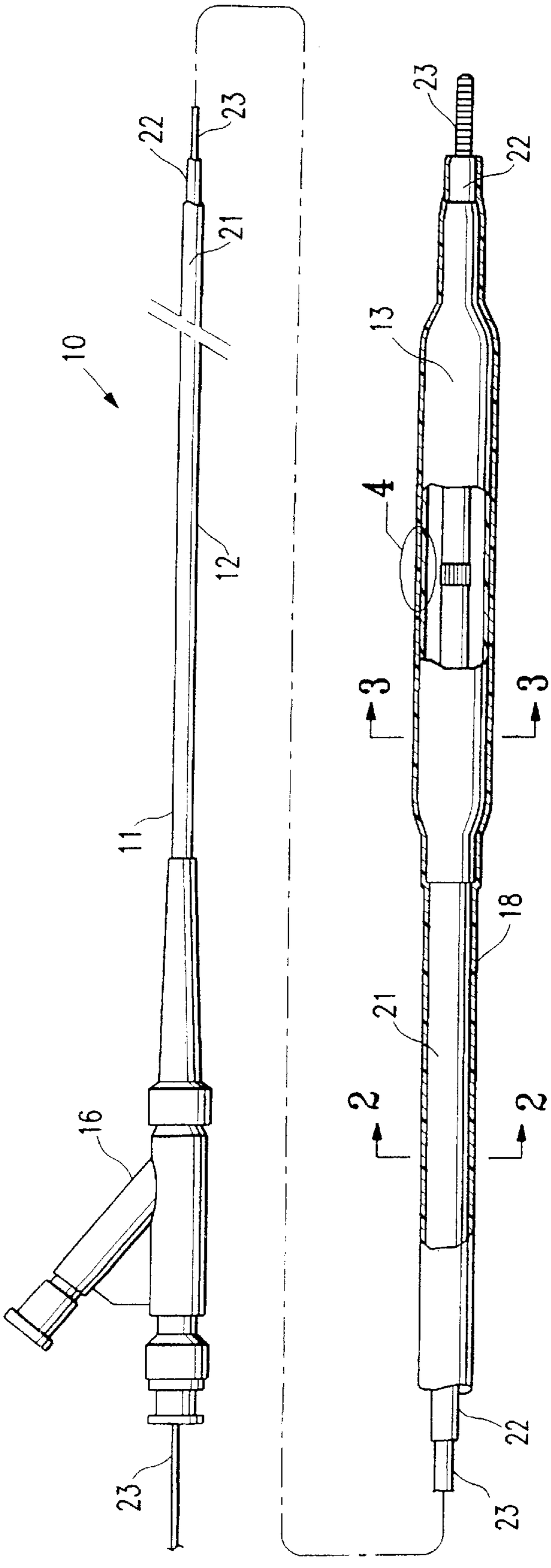


FIG. 1

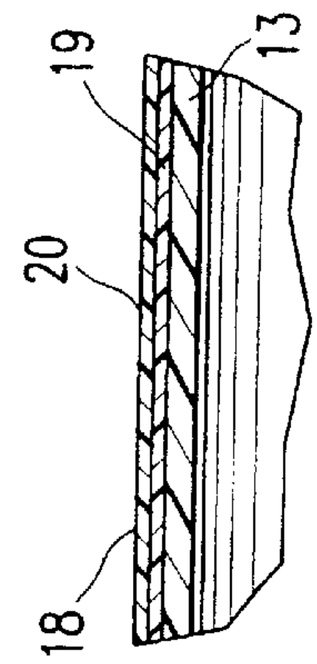


FIG. 4

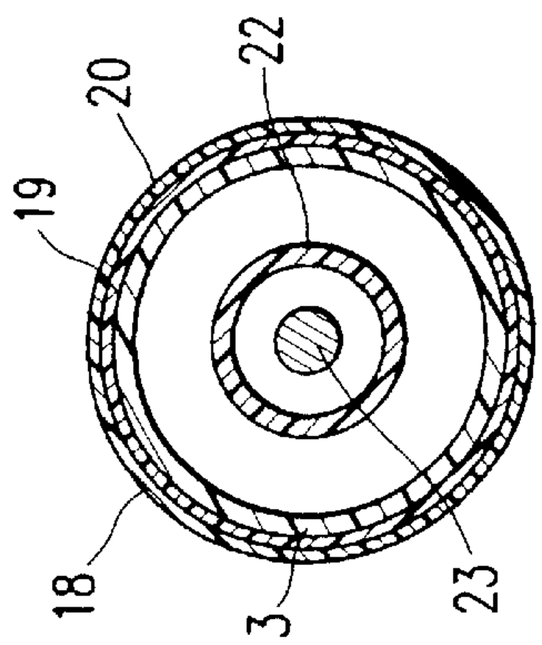


FIG. 3

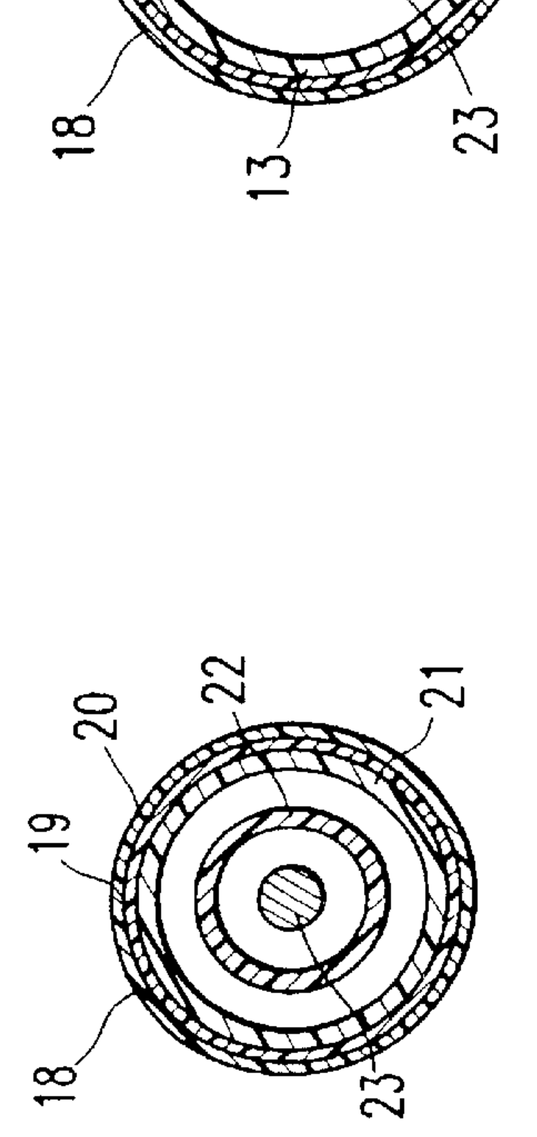


FIG. 2

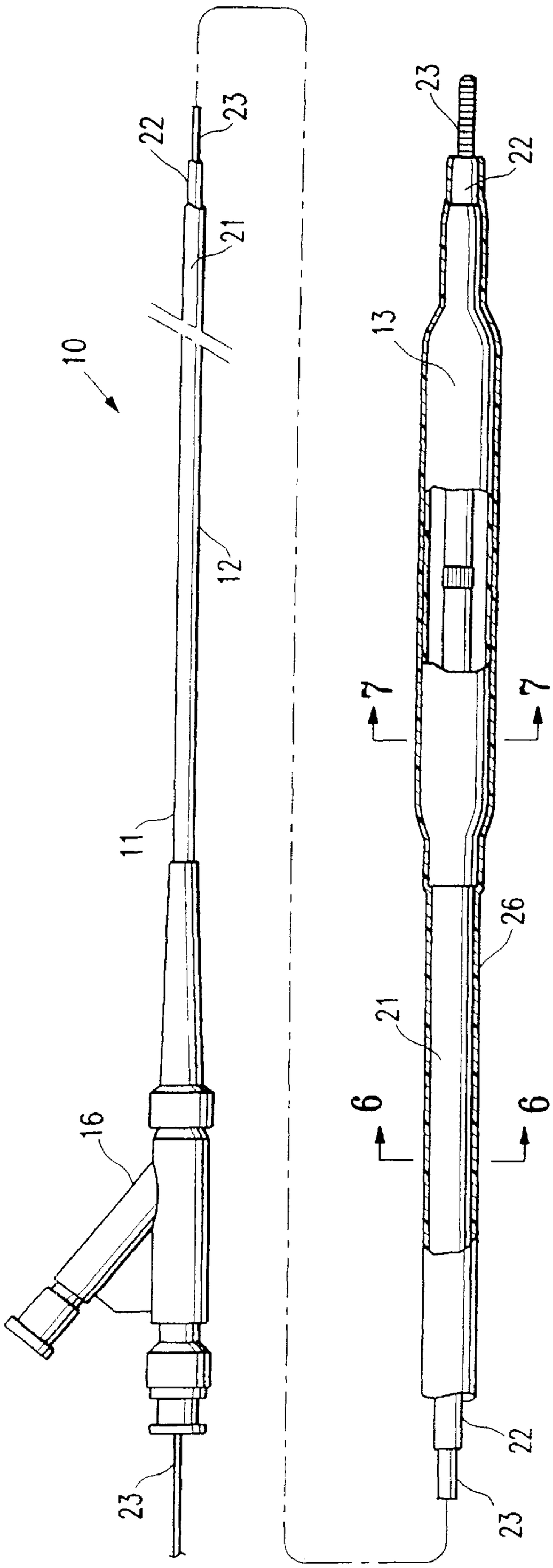


FIG. 5

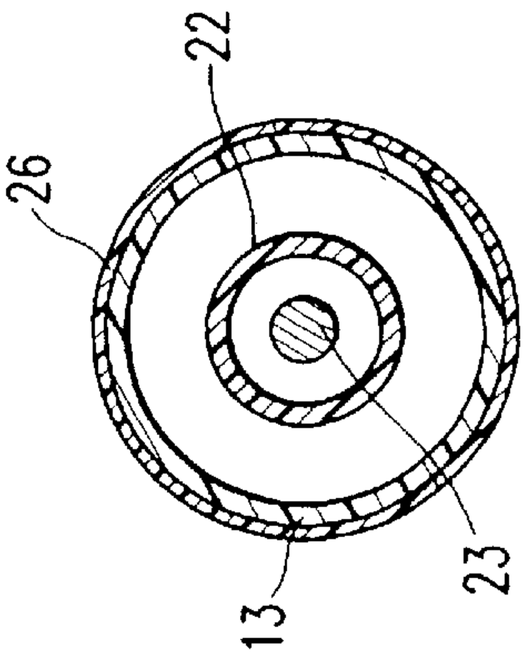


FIG. 7

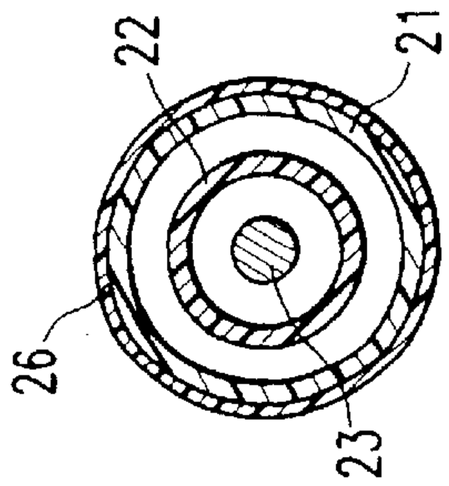


FIG. 6

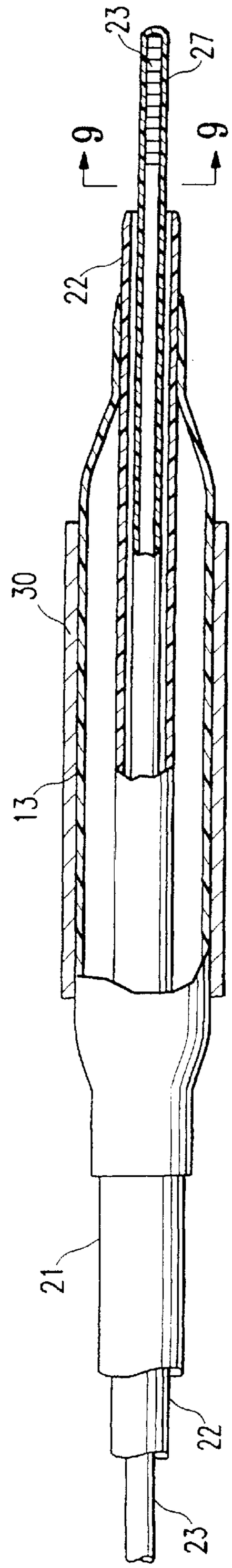


FIG. 8

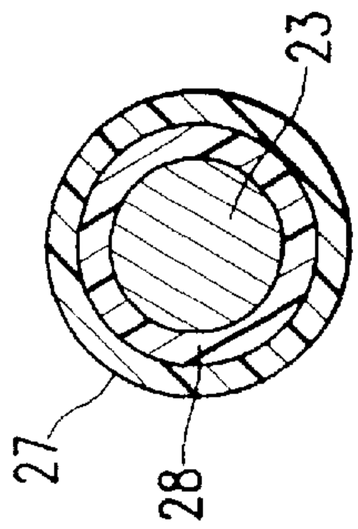


FIG. 9

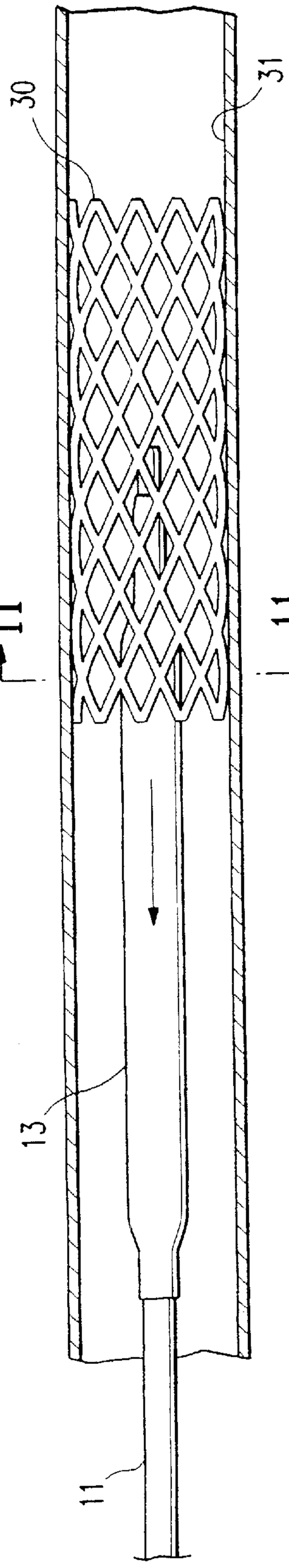


FIG. 10

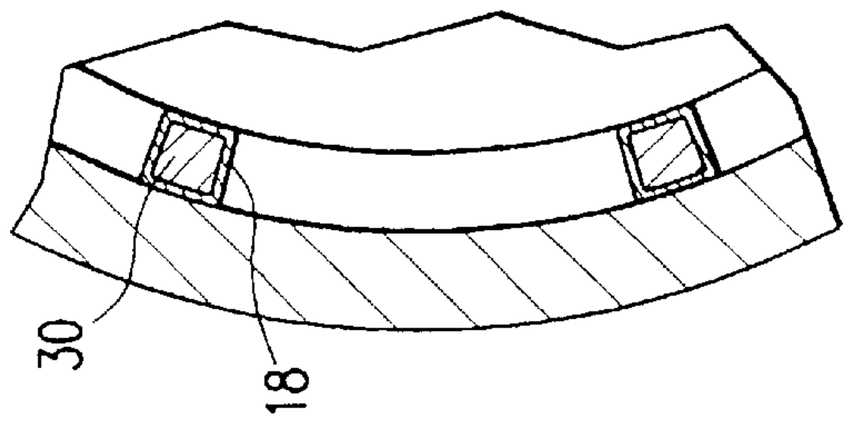


FIG. 12

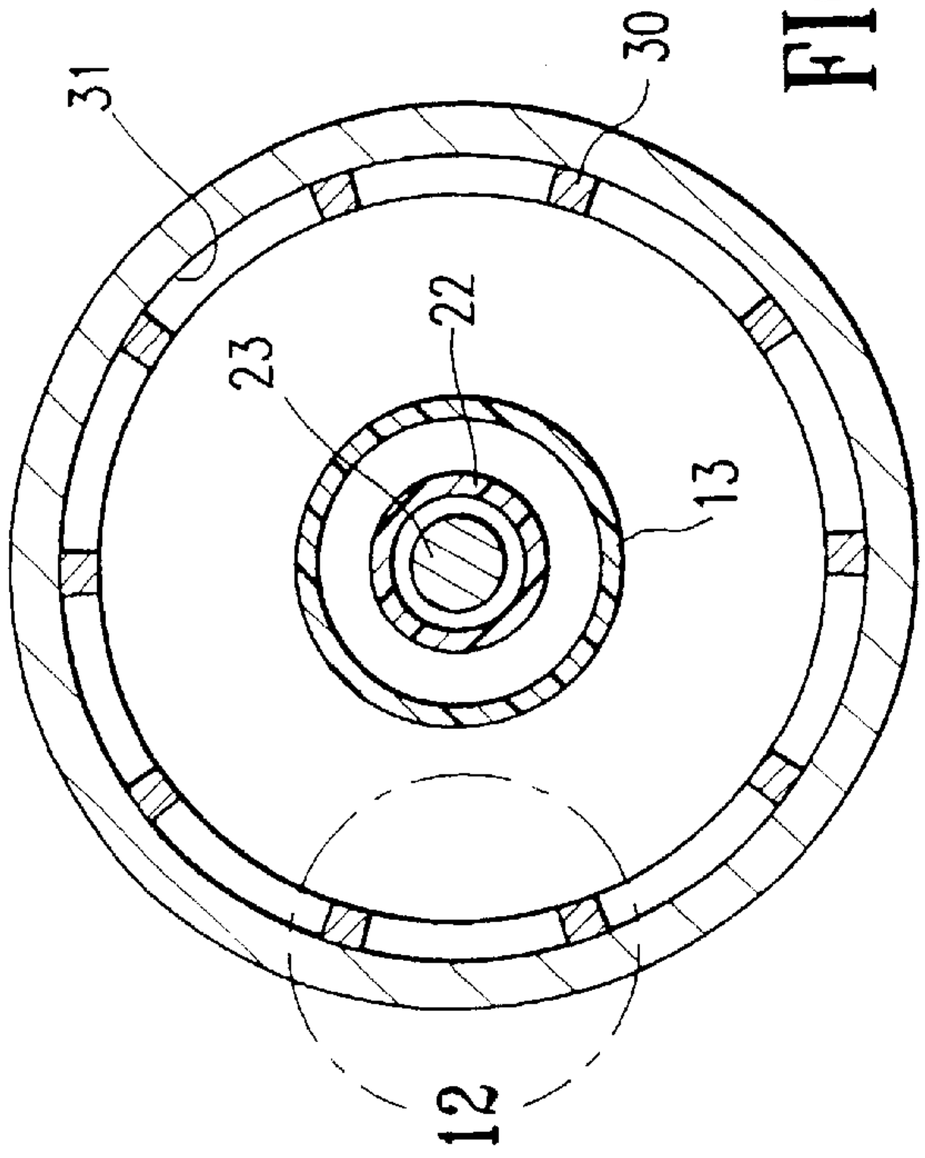


FIG. 11

SUPEROXIDE DISMUTASE OR SUPEROXIDE DISMUTASE MIMIC COATING FOR AN INTRACORPOREAL MEDICAL DEVICE

This is a continuation-in-part application of prior pending U.S. application Ser. No. 09/240,914, now U.S. Pat. No. 6,287,285 B1,Therapeutic, Diagnostic, or Hydrophilic Coating for an Intracorporeal Medical Device, filed Jan. 29, 1999, which is a continuation-in-part application of U.S. application Ser. No. 09/016,694, now U.S. Pat. No. 6,221, 425 B1, Lubricious Hydrophilic Coating for an Intracorporeal Medical Device, filed Jan. 30, 1998, the disclosures of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

This invention relates to the field of therapeutic, diagnostic, or hydrophilic coatings for intracorporeal medical devices.

The use of a medical device within a patient may be facilitated by the presence of a therapeutic, diagnostic, or hydrophilic agent on the device surface. For example, intravascular devices, such as catheters and guidewires, are more easily maneuvered within a patient's vasculature when the friction between the walls of the vessel and the intravascular device is reduced. The friction may be reduced by coating the device with a hydrophilic compound which becomes slippery after adsorbing an appreciable amount of water. Consequently, the hydrophilic coating provides lubricity when the coated device is exposed to aqueous solution, as when the coated device is exposed to water prior to insertion in the patient or to the patient's blood during use. Alternatively, coatings, such as fluoropolymers, and silicone, provide lubricity to the surface of an intracorporeal device without the need for exposure to aqueous solution. However, the degree of lubricity may vary greatly depending on the nature of the lubricious coating. Hydrophilic coatings provide superior lubricity compared to hydrophobic coatings, such as silicone, when tested against a biological tissue countersurface.

In addition to lowering the coefficient of friction of the coated device, an effective lubricious coating must strongly adhere to the device surface. The lubricious coating should remain adhered to the device surface during potentially extended periods of storage, as well as in response to abrasive forces encountered during preparation and use. Poor adhesive strength is undesirable because the lost coating may be left behind inside the patient during use, with detrimental affects and a corresponding decrease in the lubricity of the device. Typically, a trade off exists between a coating's lubricity and the coating's adhesive and cohesive strength, so that attempts to increase the adhesive strength of lubricious coatings may inadvertently decrease the lubricity of the coating. Consequently, one difficulty has been providing a highly lubricious coating that strongly adheres to a device surface.

In angioplasty procedures, there may be restenosis of the artery, i.e. reformation of the arterial blockage, which necessitates either another angioplasty procedure, or some other method of repairing or strengthening the dilated area. One difficulty has been the treatment of restenosis following an angioplasty procedure. Various medical devices, such as stents or catheters, have been coated with therapeutic or diagnostic agents, to provide localized and possibly extended exposure of the tissue to the agent. For example,

drugs which prevent the proliferation of smooth muscle cells, or which promote the attachment of endothelial cells, can be coated on a stent which is then implanted at the site of a stenosis within a patient's blood vessel, to thereby inhibit restenosis following an angioplasty or stent implantation procedure. However, the agent must be strongly adhered to the device surface for effective delivery within the patient. Moreover, controlled release of the agent from the device surface within the patient may be required as part of the therapeutic or diagnostic regime.

Another therapeutic challenge is the stabilization of vulnerable plaque. The term "vulnerable plaque" refers to an atherosclerotic plaque which may rupture and/or erode, with subsequent thrombosis. The most common type of vulnerable plaque contains a core filled with lipid, cholesterol crystals and cholesterol esters, macrophages, and other cells, having a fibrous cap which can become weakened. When ruptured, the luminal blood becomes exposed to highly thrombogenic core material, such as tissue factor (TF), which can result in total thrombotic occlusion of the artery. There is increasing evidence that the propensity of an atherosclerotic plaque to rupture is related to activity of matrix metalloproteinases (MMPs), largely synthesized by macrophage-derived foam cells. Specifically, MMPs may degrade extracellular matrix proteins such as Types I and III collagen which are a signifcant source of fibrous cap structural integrity. Thus, chronic and/or local inflammation, typically a result of monocyte adhesion, in the plaque can lead to destabilization of these vulnerable plaques and lead to acute coronary syndromes (via thrombosis).

It would be a significant advance to provide a hydrophilic coating which strongly adheres to a surface of a medical device, or a therapeutic or diagnostic coating strongly, but potentially releasably, adhered to the surface of a medical device. The present invention satisfies these and other needs.

SUMMARY OF THE INVENTION

The invention is directed to a method of providing a coating on an intracorporeal medical device, and the coated medical device, or component thereof, produced thereby. A durable coating is provided on the medical device which modifies the device surface with a therapeutic, diagnostic, lubricious or other active agent. The coating of the invention may be used on a variety of medical devices including stents, catheters, guidewires, cardiac pacing leads, vascular grafts, and the like.

In one embodiment, the coating on the intracorporeal medical device generally includes a base coat and a top coat. The base coat has a binding component and a grafting component, and is used to strongly adhere to the surface of the device and also to strongly bond to the top coat. Specifically, the binding component binds to both the top coat and to the grafting component, and the grafting component adheres to the device surface. The base coat containing the grafting component and binding component in a suitable carrier such as a solution is first applied to the surface of the device. The base coat is preferably polymerized, e.g., exposed to polymerizing radiation to polymerize the grafting component, and the grafting component is bonded to the binding component and adhered to the surface of the device to form a base coat on the device. The device is then coated with a top coat containing a desired therapeutic, diagnostic, or hydrophilic agent. The top coat may be applied in a solution which is allowed to evaporate, to form a top coat with a therapeutic, diagnostic, or hydrophilic agent. In another embodiment, the device is

coated with a top coat comprising a linking agent, and the linking agent is exposed to the therapeutic, diagnostic, or hydrophilic agent to form a complex therewith, to thereby form the therapeutic, diagnostic or hydrophilic coating of the invention. Because the top coat bonds to the base coat, the therapeutic, diagnostic, or hydrophilic coating produced will not readily wear off.

In one embodiment, the base coat comprises a binding component which is a homofunctional compound having homofunctional groups which covalently bond to functional groups in the top coat. In a preferred embodiment, the homofunctional binding component is grafted to the grafting component by a hydrogen abstraction mechanism, in which the grafting component is activated by initiators and covalently bonds to the binding component. In another embodiment, the base coat comprises a binding component which is a heterofunctional compound having a first functional group for covalently bonding with the grafting component, and a second functional group for covalently bonding to functional groups in the top coat.

As mentioned above, the binding component of the base coat bonds to the top coat. In one embodiment, the therapeutic, diagnostic, hydrophilic or other active agent has functional groups which directly bond to functional groups of the binding component. In another embodiment, the therapeutic, diagnostic, or hydrophilic agent is bound to the binding component by a linking agent in the top coat. The linking agent may inherently have functional groups, or may be modified to include functional groups, which bond to functional groups of the binding component. The linking agent may be bound to the base coat and thereafter exposed to the therapeutic, diagnostic or hydrophilic agent, or alternatively, the linking agent may be exposed to the agent before or during the binding of the linking agent to the base coat.

A variety of suitable linking agents may be used, including avidin-biotin complexes, and functionalized liposomes and microsponges and microspheres. Avidin is a polypeptide composed of at least 128 amino acid residues. Typically however, the single polypeptide chain is a subunit associated with three essentially identical polypeptide chains, forming a tetramer. Avidin as a receptor is typically used in conjunction with its highly specific ligand, biotin, $C_{10}H_{16}N_2O_3S$. An avidin tetramer will bind 4 biotin molecules in solution in a noncovalent interaction which has a binding constant of about 10^{15} M^{-1}, a half-life in vivo of about 89 days, and which is essentially undisturbed by organic solvents. Biotinylation, or the process of covalently binding biotin to another molecule, typically takes place by N-hydroxysuccinimide binding. Spacer molecules may be inserted between the avidin and the base coat, or between the biotin and the therapeutic or diagnostic agent, as is known in the art, to facilitate avidin-biotin binding or improve the activity of the therapeutic or diagnostic agent. The avidin or the biotin molecule may be chemically altered to decrease the binding constant, to thereby tailor the dissociation rate in vivo, and provide controlled release of the therapeutic or diagnostic agent bound thereto. Avidin and biotin are available from a variety of commercial suppliers, such as Sigma. In one embodiment, avidin covalently binds to the binding component of the base coat, and binds to a biotinylated therapeutic or diagnostic agent, such as a biotinylated protein, antibody, peptide or oligonucleotide. However, the avidin-biotin linking agent may alternatively have biotin moieties covalently bound to the binding component of the base coat, and avidin moieties bound to the therapeutic or diagnostic agent. Alternatively, biotin may be covalently bound to the base coat and to the therapeutic or diagnostic agent, with avidin, by virtue of its multivalency with biotin, binding the two biotin moieties together.

Liposomes are lipid molecules formed into a typically spherically shaped arrangement defining aqueous and membranal inner compartments. Liposomes can be used to encapsulate compounds such as therapeutic and diagnostic agents within the inner compartments, and deliver such agents to desired sites within a patient. The agents contained by the liposome may be released by the liposome and incorporated into the patient's cells, as for example, by virtue of the similarity of the liposome to the lipid bilayer that makes up the cell membrane. A variety of suitable liposomes may be used, including those available from NeXstar Pharmaceuticals or Liposome, Inc, if functionalized as by the procedures described herein.

Microsponges are high surface area polymeric spheres having a network of cavities which may contain compounds such as therapeutic or diagnostic agents. The microsponges are typically synthesized by aqueous suspension polymerization using vinyl and acrylic monomers. The monomers may be mono or difunctional, so that the polymerized spheres may be cross-linked, thus providing shape stability. Process conditions and monomer selection can be varied to tailor properties such as pore volume and solvent swellability, and the microsponges may be synthesized in a controlled range of mean diameters, including small diameters of about 2 micrometers or less. A standard bead composition would be a copolymer of styrene and di-vinyl benzene (DVB). The agents contained by the polymeric microsponges may be gradually released therefrom within the patient due to mechanical or thermal stress or sonication. A variety of suitable microsponges may be used, including those available from Advanced Polymer Systems, if functionalized as by the procedures described herein.

A variety of suitable therapeutic, diagnostic or hydrophilic agents may be used. For example, the therapeutic or diagnostic agent may be selected from the group consisting of proteins; peptides; oligonucleotides; antisense oligonucleotides; cellular adhesion promoting proteins or peptides including extracellular matrix proteins; polysaccharides such as heparin, hirudin, hyaluronan, and chondrotin; nitric oxide donating compounds; growth factor such as VEGF; Taxol; Paclitaxel; Carboplatin; and Cisplaten.

The therapeutic or diagnostic agents may be used for a variety of purposes, including improving the biocompatibility of the intracorporeal medical device and inhibiting restenosis. For example, antisense oligonucleotides may be used to improve biocompatibility of the medical device, or to inhibit or prevent restenosis, where the antisense oligonucleotide inhibits cell migration, inhibits synthesis of extracellular matrix proteins or growth factors, or induces apoptosis. Suitable antisense oligonucleotides are include those described in U.S. Pat. Nos. 5,470,307, 5,593,974, and 5,756,476, and Uhlmann, E. et al, Antisense Oligonucleotides: A New Therapeutic Principle, Chemical Reviews, 90(4), 544–579 (1990), incorporated by reference in their entireties. The antisense oligonucleotides may be modified with avidin or biotin, or to contain hydrophobic groups such as cholesterol, to facilitate cellular uptake and prevent degradation by nucleases. Similarly, extracellular matrix proteins may be used to improve biocompatibility of the medical device, or inhibit or prevent restenosis. Extracellular matrix proteins, such as fibronectin, laminin, collagen, and vitronectin, or synthetic peptide analogues of extracellular matrix proteins, have an amino acid sequence which contributes to cell adhesion. Synthetic peptide analogues of

extracellular matrix proteins can also be used which retain the biological function but have a lower molecular weight and different solution properties. The extracellular matrix proteins or peptides will attract migrating cells within the patient, and thus inhibit restenosis by preventing the cells from accumulating in the arterial lumen. Additionally, by attracting migrating cells, they facilitate integration with tissue of implanted devices, such as stents, and wound healing, and the uptake by cells of other therapeutic agents bound to the device surface. Additionally, the extracellular matrix proteins bound to the device surface may facilitate in vitro seeding of endothelial cells to the device prior to implantation or introduction of the device within the patient. In one embodiment, the extracellular matrix protein vitronectin is bound to the device surface, and an antibody to the B1 integrin subunit is bound to the device surface or is delivered locally or systemically. This antibody has been shown to block cellular adhesion to all extracellular matrix proteins except vitronectin, thereby enhancing the adhesive power of the modified device surface. Similarly, nitric oxide donor drugs may be used to improve biocompatibility of a medical device, and may also prevent or inhibit platelet aggregation and promote wound healing. Additionally, nitric oxide donor drugs may be used as a vasodilator relaxing smooth muscles of a vessel prior to, during, and/or after angioplasty or stent placement. A variety of suitable nitric oxide donor drugs can be used including nitric oxide-polyamine complexes, 2-methyl-2-nitrosopropane, S-Nitroso-N-acetyl-D,L-penicillamine, 3-morpholoinosydoimine, sodium nitrate, s-nitrosoglutathione, sodium nitroprusside, and nitroglycerine. The structure and mechanisms of suitable nitric oxide donor drugs are disclosed in U.S. Pat. No. 5,650,447, incorporated by reference in its entirety.

In one embodiment, the therapeutic agent is superoxide dismutase or a superoxide dismutase mimic (i.e., mimetic). Superoxide dismutase is an endogenous enzyme which catalytically converts superoxide to hydrogen peroxide and oxygen. Superoxide is a highly oxidative species present in disease states, which reacts with endogenous nitric oxide (NO) to produce the oxidative species peroxynitrite, a cell damaging oxidative species which also causes lipid peroxidation. Moreover, superoxide consequently lowers the endogenous NO concentration. Endogenous NO has a number of beneficial effects, and one aspect of the invention is a method of preventing or inhibiting the removal of endogenous NO by superoxide, to, for example, prevent or inhibit restenosis, and to stabilize a vulnerable plaque from erosion and/or rupture and thrombosis. In a presently preferred embodiment of the invention, the superoxide or a superoxide mimic has a pendant functional ligand which covalently bonds to a compatible reactive group of a coating component on a surface of a medical device. The terminology "superoxide mimic" should be understood to refer to compound which mimics the action of superoxide by, for example, catalytically dismutating superoxide.

In one embodiment, superoxide dismutase or a superoxide dismutase mimic is presented on a surface of the medical device to prevent or inhibit restenosis, at least in part by preserving endogenous NO. Benefits of endogenous NO which are believed to prevent or inhibit restenosis include vasorelaxation, inhibition of smooth muscle cell migration and extra-cellular matrix synthesis, and inhibition of platelet and inflammatory cell aggregation and adhesion. In another embodiment, superoxide dismutase or a superoxide dismutase mimic is presented on a surface of the medical device to prevent or inhibit rupture and/or erosion of vulnerable plaque, at least in part by preserving endogenous NO. NO has been shown to reduce monocyte adhesion. Thus, by reducing monocyte adhesion, fewer macrophage-derived foam cells and fewer MMPs would be present, resulting in stabilization of the plaque. In one embodiment, the vulnerable plaque is stabilized with a stent or catheter device having a superoxide dismutase or a superoxide dismutase mimic coating of the invention to inhibit or prevent inflammation and resulting thrombosis processes.

A variety of suitable hydrophilic or lubricious compounds can be used as the hydrophilic agent. The hydrophilic agent typically has functional groups which directly bond to the binding component of the base coat. Because the hydrophilic compound is bound to the base coat, it will not readily wear off even after repeated hydration and abrasion. To hydrate the hydrophilic coating on the device and render the coating highly lubricious, the coated device may be exposed to aqueous fluid either before insertion into a patient or by contact with body fluid while inside the patient.

In another embodiment, a base coat is not used, and a coating is provided on the intracorporeal medical device, which in a presently preferred embodiment is a hydrophilic coating generally including a hydrophilic polymer, an ionic compound with at least one inorganic ion, and a grafting component. The grafting component is polymerized as outlined above, so that the grafting component grafts to the device and crosslinks to the hydrophilic polymer, to form a hydrophilic coating on the device. When the coated device is hydrated, the coating absorbs water and is highly lubricious, but does not dissolve in the aqueous or blood medium because the hydrophilic polymer is immobilized by the grafted network. Moreover, the ionic compound, or salt, increases the lubricity of the hydrophilic coating by providing uncrosslinked domains in the crosslinked matrix. Because the ability of a hydrophilic polymer to absorb water is decreased when the polymer is crosslinked, the salt enhances the polymer lubricity by disrupting the crosslinking of the hydrophilic polymer into the grafting component crosslinked network. Therefore, when the hydrophilic coating is hydrated by exposure to a solvent and the salt dissolves, these uncrosslinked domains provide additional lubricity by increasing the contact between the hydrophilic polymer and the countersurface, e.g. the patient's vessel wall, and hence additional lubricity. Additionally, the salt affects morphology of the hydrophilic compound, resulting in improved resistance to particle shedding from the coated device.

The coating of the invention can be applied to any device having a polymeric surface, as for example, a catheter formed of conventional materials, or a metal device, such as a metal guidewire or stent, having a polymer primer coat. For example, the catheter components may be formed of high density polyethylene, polyethylene terephthalate, and polyolephinic ionomers such as Surlyn®, nylon and the like which are frequently used to form dilatation balloons or catheter shafts. Additionally, the therapeutic, diagnostic, or hydrophilic coating of the invention can be applied directly to a metal device. For example, in the embodiment of the invention having a base coat and a top coat, the base coat adheres, as by Van der Waals forces, to the metal surface of the device, so that a polymeric primer coat need not be used.

In the embodiment of the coating of the invention having a hydrophilic agent, the coated device has a superior hydrophilic coating which is highly lubricious against biological tissue and is strongly bound to the device surface due to the grafting component used alone or in combination with the binding component. In the case of a PTCA catheter or

guidewire, the coating serves to enhance device access to distal lesions and the ease with which a device crosses small diameter athlerosclerotic lesions.

In the embodiment of the coating of the invention having a therapeutic or diagnostic agent bound to the medical device surface, directly or via a linking agent, the coating of the invention provides localized delivery of the therapeutic or diagnostic agent. Similarly, the coating of the invention improves the residence time of the therapeutic or diagnostic agent. By binding the agent to the device, the rapid clearance from the bloodstream of the therapeutic agent, as for example when the body's immune system phagocytizes the therapeutic agent or a liposome containing the agent, is avoided.

These and other advantages of the invention will become more apparent from the following detailed description of the invention and the accompanying exemplary drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an elevational view, partially in section, of a dilatation catheter having a coating of the invention.

FIGS. **2** and **3** are transverse cross sections of the catheter shown in FIG. **1** taken along lines **2—2** and **3—3**, respectively.

FIG. **4** is an enlarged longitudinal cross-sectional view of the coated catheter shown in FIG. **1** within the circle **4**.

FIG. **5** is an elevational view, partially in section, of a dilatation catheter having a coating of the invention.

FIGS. **6** and **7** are transverse cross sections of the catheter shown in FIG. **5** taken along lines **6—6** and **7—7**, respectively.

FIG. **8** is a longitudinal cross section of a guidewire having a coating of the invention.

FIG. **9** is a transverse cross section of the guidewire shown in FIG. **8** taken along lines **9—9**.

FIG. **10** is an elevational view of a stent having a coating of the invention, with a balloon catheter, within a body lumen.

FIG. **11** is a transverse cross sectional view of the stent and catheter shown in FIG. **10**, taken along lines **11—11**.

FIG. **12** is an enlarged view of the stent shown in FIG. **11** within the circle **12**, illustrating the coating on the stent.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the invention, shown in FIG. **1**, the intracorporeal medical device having a coating of the invention **10** is a balloon catheter **11**, generally including an elongated catheter shaft **12**, with an inflatable balloon **13** on the distal end and an adapter mounted **16** on the proximal end. The catheter shaft **11** and balloon **13** are provided with a coating **18** with a therapeutic, diagnostic, lubricious, or other active agent. As best shown in FIG. **4**, illustrating an enlarged longitudinal cross section of the coating **18** shown in FIG. **1** within circle **4**, the coating comprises a base coat **19** and a top coat **20**. FIGS. **2** and **3** illustrate a transverse cross section of the catheter of FIG. **1** taken along lines **2—2** and **3—3**, respectively. The catheter shaft may comprise an outer tubular member **21**, and an inner tubular member **22** disposed in a lumen of the outer tubular member and having a lumen configured to slidably receive a guidewire **23**.

In the embodiment illustrated in FIGS. **1–4** in which the therapeutic, diagnostic, or hydrophilic coating comprises a base coat **19** and a top coat **20**, the base coat has a grafting component and a binding component. The grafting component is selected from the group consisting of vinyl compounds, acrylate compounds, and allyl compounds, such as any oligomer or monomer with one or more vinyl, acrylate or allyl double bonds. Exemplary of the vinyl compounds are di-vinyl benzene, n-vinyl pyrrolidone, and triethylene glycol divinyl ether. Exemplary of the acrylate compounds are tri-methylol propane tri-acrylate, pentaerythritol tetra-acrylate, and Bisphenol A. ethoxylate diacrylate. Exemplary of the allyl compounds are allyl ether, di-allyl maleate, and tri-allyl isocyanurate.

To form the base coat **19**, the grafting component is blended with a binding component. The binding component and a compound in the top coat **20** have functional groups capable of binding to one another, so that the top coat will be securely bound to the medical device through covalent attachment to the binding component. In one embodiment, the top coat **20** comprises a therapeutic, diagnostic or hydrophilic agent which bonds to the functional groups of the binding component. In another embodiment, the top coat **20** comprises a linking agent which bonds to the binding component, and which forms a complex with a therapeutic, diagnostic or hydrophilic agent to thereby bond the agent to the medical device. In a presently preferred embodiment, the linking agent is selected from the group consisting of avidin-biotin complexes, microsponges, and liposomes. The complex of the linking agent and the therapeutic, diagnostic or hydrophilic agent may be formed by a bond between the linking and the therapeutic, diagnostic or hydrophilic agents, as in the case of an avidin-biotin linking agent. Alternatively, the complex may be formed by the encapsulation or containment of the therapeutic, diagnostic or hydrophilic agent by the linking agent, as in the case of a liposome, microsponge, or microsphere linking agent.

In a presently preferred embodiment, the binding component comprises a homodi- or homotri-functional monomer with a functional group for binding to the functional group of the top coat, or a heterodifunctional monomer with a first functional group for binding to the functional group of the top coat and a second functional group for binding to the functional group of the grafting component of the base coat. The nature of the functional groups of the binding component varies depending on the identity of the functional groups of the top coat **20** that will be applied thereto. The binding component has one or more functional groups selected from the group consisting of aziridine, carbodiimide, aldehyde, isocyanate, succinimide, maleimide, oxirane, and carboxyl derivatized with carbodiimide or tresyl or succinimide.

In one embodiment, the binding component is selected from the group consisting of polyaziridine and polycarbodiimide resin compounds, and the top coat has carboxyl groups capable of binding to the binding component. The top coat may also have an amine group in the case of a carbodiimide resin binding component. Exemplary of the polyaziridine compounds are tri-aziridine oligomer, such as Zeneca cx-100, available from Zeneca Resins. Exemplary of the carbodiimide compounds are XL-29SE available from Union Carbide. The hydrophilic agent is a polymer showing appreciable water absorption and containing carboxyl groups, including but not limited to, polyacrylic acid, alginic acid, carboxy methyl cellulose, and hyaluronic acid. The carboxy hydrophilic coating may be exposed to a basic solution, such as 0.1 N potassium or sodium hydroxide, to neutralize free carboxyl groups on the hydrophilic coating, and the coating then rinsed in water to remove the basic solution. Exemplary of the therapeutic or diagnostic agents

having carboxy functional groups are proteins, peptide, antisense and sense oligonucleotides, and carboxy functional drugs.

In another embodiment, the binding component comprises an aldehyde compound and the top coat is a compound having amine groups. The binding component may be a homodi- or homotri-functional monomers having aldehyde groups, such as glutaraldehyde and acrolein. Alternatively, the binding component may be a heterodifunctional monomers having a first functional group and a second functional group, the first functional group being aldehyde groups, and the second functional group being groups such as vinyl groups. Exemplary of such heterodifunctional compounds are cinnamaldehyde. Exemplary of the hydrophilic agent are a (co)monomer selected from the group consisting of 2-aminoethyl acrylate, 2-aminoethyl methacrylate, and N-(3-aminopropyl)methacrylamide; or a polymer of at least one of said (co)monomers co-polymerized with hydrophilic monomers selected from the group consisting of acrylamide, di-methyl acrylamide, and N-vinyl pyrrolidone; or a peptide having a secondary basic group for reaction with the aldehyde of the binding component, such as arginine, glutamine, and histidine, which include but are not limited to gelatin, hirudin, and albumin; or polyethylenimine. Exemplary of the therapeutic or diagnostic agents having amine groups are peptides, proteins, nitric oxide donating compounds, antisense and sense oligonucleotides.

In another embodiment, the binding component is an isocyanate compound and the top coat is a compound containing hydroxy or amine groups. The binding component may be a homodi- or homotri-functional monomers having isocyanate groups. Exemplary of such isocyanate compounds are an isocyanate of hexamethylene diisocyanate, such as Desmodur 3300 available from Bayer, an aliphatic or aromatic isocyanate monomer, biuret or isocyanurate oligomer, or polyol or polyamine chain extended variant of such starting materials as 1,6 hexamethylene diisocyanate, isophorone diisocyanate, toluene diisocyanate, diphenylmethane-diisocyanate, bis(4-isocyanato cyclohexyl)methane. The isocyanate compound can also be the monomer or polymer made from allyl isocyanate or other such monomers. Alternatively, the binding component may be a heterodifunctional monomers, the first functional group being isocyanate groups, and the second functional group being groups such as methacrylate. Exemplary of such isocyanate compounds are isocyanatoethylmethacrylate. Exemplary of the hydrophilic agent are poly(vinyl alcohol), hydroxy propyl cellulose, hyaluronic acid, a peptide having a secondary basic group for reaction with the isocyanate of the binding component, and a copolymer blend of a first monomer selected from the group consisting of vinyl and acrylic monomers and a second monomer selected from the group consisting of hydroxy and amine monomers. Examples of the peptide include but are not limited to gelatin, hirudin, and albumin, and examples of the copolymer blend hydrophilic polymers include but are not limited to an 80/20 mixture of acrylamide and hydroxy ethyl methacrylate. Exemplary of the therapeutic or diagnostic agents having amine or hydroxyl groups are peptides, proteins, nitric oxide donating compounds, antisense and sense oligonucleotides.

In another embodiment, the binding component is a succinimide or oxirane compound and the top coat is a compound containing amine groups. The binding component may be a heterodifunctional monomers, the first functional group being succinimide or oxirane groups, and the second functional group being groups such as acrylate, methacrylate, and allyl. Examples of such compounds include N-acryloxysuccinimide, having a succinimide first group and an acrylate second group (C═CHCOOR), glycidyl methacrylate having an oxirane first group and a methacrylate second group (C═CCH_3COOR), and allyl glycidyl ether having an oxirane first group and an allyl second group (H_2C═$CHCH_2$). The top coat compounds having amine groups are as given above.

In another embodiment the binding component is a heterodifunctional monomers, the first functional group being maleimide groups, and the second functional group being groups such as vinyl (H_2C═CH). Examples of such compounds include N-(4-vinylphenyl)maleimide. The top coat compounds have thiol (SH) groups. Exemplary of such top coat compounds are peptides, proteins, nitric oxide donating compounds, antisense and sense oligonucleotides.

In another embodiment the binding component contains carboxy groups that have been derivatized. For example, a binding compound having carboxy groups can be derivatized by carbodiimide or tresyl (i.e., trifluoroethane sulfonyl) or succinimide functional compounds to provide a binding component that will covalently bind to amine groups in the top coat. Examples of derivatizing agents include 1-ethyl-3-(3-dimethylaminopropyl carbodiimide) (i.e., EDAC), and tresyl chloride. Examples of suitable carboxy containing compounds include acrylic acid, methacrylic acid, itaconic acid, ethylene acrylic acid (such as Primacor, available from Dow). The carboxy binding compounds would be applied to the medical device surface as part of a base coat as described herein, and cured. The carboxy containing compounds could be radiation or otherwise cured, except in the case of ethylene acrylic acid binding compounds where the compound is deposited on the device by a solvent solution or neutralized aqueous dispersion and cured by thermal drying to remove the solvent. Thereafter, the carboxy compounds are derivatized, as by immersing the cured base coat in a solution of the derivatizing agent, and rinsing the surface after the derivatizing reaction to remove excess agent, to form a base coat having a binding component having a functional group of carboxy that had been derivatized with carbodiimide or tresyl or succinimide. Thereafter, the derivatized surface may be immersed into a solution of the top coat having an amine functional group.

In one embodiment of the linking agent, the linking agent inherently has the functional groups outlined above for binding to the functional groups of the binding component of the base coat. For example, amine, carboxy, or hydroxy functional groups on the avidin moiety of an avidin-biotin linking agent can bind the avidin-biotin linking agent to the base coat. Additionally, where the biotin moiety of the avidin-biotin linking agent binds to the base coat, n-hydroxy succinimide ester of the biotin moiety can be used to bind the biotin to an amine or amine functionalized surface of the base coat. An amine functionalized surface can be obtain by using a monomer such as n-(3-aminopropyl) methacrylamide hydrochloride in the base coat. Alternatively, biotin can be bound to carboxyl groups on a drug or carboxyl functional surface by using biotin hydrazide per well established methods.

Alternatively, the linking agent may be modified to include the functional groups. Primary amine groups, hydroxyl, thiol, or carboxy groups can be added to liposome or microsponge linking agents to permit covalent attachment of the linking agent to the base coat functional groups. For example, compounds having the desired functional groups, such as monomers such as hydroxyethylmethacrylate having a hydroxy functional group and n-(3-aminopropyl)

methacylamide having an amine functional group, can be introduced into the bead composition during synthesis of the microsponges to form the functionalized microsponges. Functionalized microsponges can be made by the methods disclosed in U.S. Pat. No. 5,840,293. Typically, hydrophilic monomers will be used to functionalize the microsponges used in the coating of the invention. The process used for functionalizing the microsponges with hydrophilic monomers such as hydroxyethyl methacrylate, n-(3-aminopropyl) methacrylamide hydrochloride, and acrylic acid, is inverse suspension polymerization. However, when hydrophobic monomers are used, a suspension polymerization process is used. Liposomes can be functionalized by using phosphatidyl serine (di-fatty acid) or phosphatidyl ethanolamine (di-fatty acid) or a mixture of the two as the feedstock. Fatty acids can be oleic, palmitic or others. These materials will provide primary functionality, permitting binding to a basecoat containing isocyanate or aldehyde functionality. Alternatively, a carboxylated surface can be derivitized using a carbodiimide such as EDC, and this can be used to bind the functionalized liposomes.

Additionally, two different linking agents may be used to bind the therapeutic, diagnostic or hydrophilic agent to the base coat. For example, avidin-biotin may be bound to the binding component of the base coat and also to a second linking agent such as a functionalized liposome or microsponge which encapsulates a therapeutic or diagnostic agent.

In the embodiment illustrated in FIGS. **1–4**, in which the coating **18** comprises a top coat **20** on a base coat **19** having a binding and a grafting component, the method of providing a therapeutic, diagnostic or lubricious hydrophilic coating on an intracorporeal medical device of the invention comprises, applying to the medical device a solution having a binding component and a grafting component, and polymerizing the grafting component so that the grafting component grafts to the device and crosslinks with, or otherwise binds as by copolymerization or covalent bonding to, the binding component, to form the base coat **19**. The device thus coated with the base coat **19**, hereafter the base coated device, may typically be dried, either a room temperature or at elevated temperatures, to evaporate the base coat solution solvent, before polymerizing the grafting component. The base coat on the device is then coated with a solution of the top coat agent (i.e., the therapeutic, diagnostic or hydrophilic agent, or the linking agent) to form the top coat **20**. The coated device is then dried at elevated or room temperature. The top coat agent grafts via covalent bonds to the binding component, to form the coating **18** on the device. In the case of a hydrophilic agent, the coating **18** can then be hydrated by exposure to aqueous solution, rendering it highly lubricious.

In the embodiment having a linking agent, the solution of the top coat applied to the base coat comprises a linking agent that is already exposed to the therapeutic, diagnostic or hydrophilic agent or that will subsequently be exposed to the agent. The microsponge linking agents are bound to the binding component and thereafter exposed to a solution of the therapeutic, diagnostic or hydrophilic agent, to introduce the agent into the pores of the microsponge. Alternatively, the microsponge linking agent may be preloaded with the therapeutic, diagnostic or hydrophilic agent before or during bonding to the base coat. The microsponges may be exposed to the therapeutic or diagnostic agent as, for example, by immersing the microsponges into a solution of the agent before or after the microsponges are attached to the base coat, and thereafter evaporating the solvent. The avidin-biotin and liposome linking agents are typically exposed to the therapeutic, diagnostic or hydrophilic agent before being bonded to the base coat.

Polymerization of the grafting component is carried out by irradiating the base coated device with ultra-violet (UV) light or with electron beam irradiation. When UV light is used, photoinitiators must be present in the base coat solution. In the process of polymerization, the UV light induces free radicals on the photoinitiators, which transfer to the acrylate, vinyl or allyl compound of the grafting component, thereby causing the grafting component to polymerize into a crosslinked network. These processes, involving UV or electron beam irradiation, are known in the art as radiation induced acrylate/vinyl free radical polymerization. Additionally, during this process, the acrylate, vinyl or allyl network crosslinks, or otherwise binds as by copolymerization or covalent bonding, to the functional groups of the binding component, e.g. the polyaziridine or polycarbodiimide oligomers, the isocyanate containing oligomer, or the aldehyde or polyaldehyde compound, and grafts to the device polymeric surface via a hydrogen abstraction mechanism. The result is a well adhered base coat **19** containing free unreacted binding component functional groups on the surface of the coating available to graft the agent of the top coat **20**.

The photoinitiator is any compound that generates a free radical when irradiated with UV or visible light. Exemplary of the photoinitiator are benzophenone, benzoin methyl ether, 2,2 dimethoxy-2-phenylacetophenone, 1-hydroxycyclohexyl phenyl ketone, and ethyl 4-(dimethylamino)benzoate.

FIG. **5** illustrates another embodiment of the invention, in which the binding component is omitted, and the coating **26** comprises a grafting component blended with the hydrophilic agent before being applied to the device. FIGS. **6** and **7** illustrate transverse cross sections of the coated catheter shown in FIG. **5**. In this embodiment of the invention, the method of providing a lubricious hydrophilic coating on an intracorporeal medical device comprises applying to the device a solution comprising a hydrophilic polymer, an ionic compound with at least one inorganic ion, and a grafting component. The grafting component is polymerized so that the grafting component grafts to the device and crosslinks with the hydrophilic polymer, with some uncrosslinked domains remaining in the crosslinked matrix. The coated device is typically dried before exposure to the polymerizing radiation. The coated device can then be hydrated by exposure to an aqueous solution, whereby the hydrophilic polymer absorbs the solution and the salt dissolves, rendering the coating highly lubricious.

In the embodiment illustrated in FIG. **5** the hydrophilic agent is any polymer displaying appreciable water absorption, including but not limited to poly(ethylene oxide), poly(vinylpyrrolidone), poly(vinyl alcohol), poly (acrylamide), alginic acid, hyaluronic acid, poly(acrylic acid), and guar gum. The grafting component and its polymerization are as discussed in the previous embodiments. Suitable ionic compounds with at least 1 inorganic ion, i.e. a salt, include but are not limited to potassium bromide, and sodium chloride.

In another aspect of the invention in which the medical device is formed of metal, a primer coating is applied to the device before applying the therapeutic, diagnostic or hydrophilic coating. FIG. **8** illustrates a metal guidewire **23** having a primer coat **28** and a therapeutic, diagnostic or lubricious, hydrophilic coating **27** of the invention. The primer coat **28** is applied to at least the entire length of the guidewire to be

coated with the therapeutic, diagnostic or hydrophilic coating. The polymerized primer coating **28** is selected from the group consisting of vinyl, acrylate and allyl compounds. The vinyl or acrylate compounds of the primer and the polymerization of these compounds are as discussed above for the grafting components. FIG. **9** illustrates a transverse cross section of the guidewire shown in FIG. **8** along lines **9—9**. In the presently preferred embodiment illustrated in FIG. **8**, the coating **27** is a hydrophilic coating which is the same as coating **26**, comprising a grafting component blended directly with a hydrophilic agent and an ionic compound with at least one inorganic ion. In the method of the invention, a solution comprising the primer coating is applied to the guidewire **23**, and primer coat **28** is typically dried before the vinyl or acrylate compound is polymerized. A solution comprising the hydrophilic agent and grafting component is then applied to the primer coat and exposed to polymerizing radiation, to form the hydrophilic coating **27** on the guidewire. However, the coating **27** may comprise the therapeutic, diagnostic or hydrophilic coating **18** having a base coat **19** and top coat **20** as discussed above, and, in which case, the primer coat **28** may be omitted.

In another embodiment of the invention, illustrated in FIGS. **8** and **10–12**, the therapeutic, diagnostic, or hydrophilic coating of the invention is applied to a prosthesis, such as an intravascular stent. FIG. **8** illustrates a stent **30** on a balloon **13** of a balloon catheter **11** for introduction into a patient's vasculature. FIG. **10** illustrates the stent after being implanted within the patient's vessel **31**. Typically, the stent is expanded within the patients vessel **31** by inflation of the balloon **13**, the balloon deflated and the balloon catheter withdrawn, leaving the stent implanted in the vessel. FIG. **11** illustrates a transverse cross sectional view of the stent, and catheter, shown in FIG. **10**, taken along lines **11—11**. The stent is coated with a diagnostic, therapeutic, or hydrophilic coating of the invention, as illustrated in more detail in FIG. **12**, showing an enlarged view of the stent shown in FIG. **11**, within circle **12**. In a presently preferred embodiment, the stent is coated with a therapeutic coating of the invention, such as a therapeutic agent to inhibit or prevent restenosis, using the coating **18** comprising base coat **19** and top coat **20**. In a presently preferred embodiment, the restenosis therapeutic agent is a peptide or protein, or a nitric oxide donating compound.

In one embodiment, superoxide dismutase (SOD) or a superoxide dismutase mimic (SODm) is covalently attached to a medical device. SODm are presently preferred over SOD because they are more effective on a weight basis, have a higher reaction rate, are not enzymatically degraded in-vivo, and are more easily sterilizable than SOD, as for example by electron beam sterilization. Examples of suitable SODm can be found in U.S. Pat. Nos. 5,874,421 (Riley et al.); 5,610,293 (Riley et al.); 5,637,578 (Riley et al.), and 6,084,093 (Riley et al.); and PCT Application WO 97/33588, incorporated by reference herein in their entireties. A presently preferred SODm is a manganese complex of a macrocyclic polyamine ring, and more specifically a low molecular weight synthetic manganese heterocyclic, available from MetaPhore Pharmaceuticals. Presently preferred manganese-based SODm available from MetaPhore Pharmaceuticals include grade RM 35-4 and M-40470. Specifically, presently preferred SODm are [Manganese(II) dichloro{24-[2-aminoethylthio-](4R,9R,14R,19R)-3,10,13, 20,26-pentaazatetracyclo[20.3.1.$0^{4,9}$ 0.$0^{14,19}$]hexacosa-1 (26),22(23),24-triene (i.e., $C_{23}H_{40}N_6Cl_2SMn$). Although the presently preferred SODm are manganese complexes, other metal complexes may be used including iron complexes, and zinc complexes.

In a presently preferred embodiment, one or more pendant ligands which present a binding functionality are present on the SOD or SODm for covalent attachment to the device. The pendant ligand functionality is preferably an amine group. Details of suitable amine pendant ligands can be found in K. Udipi et al, Modification of inflammatory response to implanted biomedical materials in vivo by surface bound superoxide dismutase mimic, J. Biomed. Mater. Res.; 51(4): 549–560, (2000), and specifically in FIG. **1** therein, incorporated by reference in its entirety. However, a variety of suitable pendant ligand functionalities can be used including hydroxyl and thiol groups.

The covalent attachment of the SOD or SODm will occur by reaction of a functional group on the SOD or SODm, such as a pendant functional ligand as discussed above, with a compatible reactive group of a base coat. In one embodiment, the base coat is base coat **19** comprising a binding component and a grafting component as discussed above in relation to the attachment of a therapeutic, diagnostic or hydrophilic top coat to the device. Thus, the SOD or SODm is covalently bound to the compatible reactive group (i.e., binding component) of the base coat, and the compatible reactive group is covalently linked to the surface and bulk of a coating (i.e., grafting component) on the device. In a presently preferred embodiment, the binding component functional group is selected from the group consisting of isocyanate, aldehyde, oxirane, succinimide, maleimide, acetoacetoxy, aziridine, carbodiimide, and acid chloride (i.e., RCOCl). The grafting component, as discussed above, generally comprises a compound selected from the group consisting of vinyl, acrylate, and allyl compounds, adhered to the device and bonded to the binding component. In a presently preferred embodiment, if the SOD or SODm pendant ligand contains a primary amine, then the binding component functional group is an isocyanate, aldehyde, oxirane, N-hydroxy succinimide, or acetoacetoxy functionality. Examples or monomers containing these groups are dimethyl meta-isopropenyl benzyl isocyanate, cinnamaldehyde, glycidyl methacrylate, N-acryloxysuccinimide, and acetoacetoxy ethylmethacrylate. If the SOD or SODm pendant ligand contains a hydroxyl group, then an isocyanate monomer can be used to form the base coat binding component. If the pendant ligand contains a thiol group, then a maleimide monomer such as N-(4vinylphenyl)maleimide can be used to form the base coat binding component. The base coat is polymerized on the device as discussed above by irradiation, and preferably by UV curing.

In one embodiment, the base coat includes a spacer, such as polyethylene glycol (PEG), which links the SOD or SODm to the binding component to improve steric mobility and to reduce the effects of plasma proteins on the coating, to provide anti-fouling.

With the SOD or SODm covalently bound to the base coat on the device, the coating provides for the presenting of SOD or a SODm for catalytically converting superoxide to hydrogen peroxide and oxygen. The coating thereby reduces the superoxide level, to treat disease states, such as restenosis and vulnerable plaque, by for example, preventing reduction of the endogenous NO level which would otherwise occur in the presence of superoxide. The SOD or SODm is typically not released from the device within the patient, but remains covalently bonded to the device. The base coat of the invention provides for attachment of SOD or SODm to a medical device, which is improved over techniques using a siloxane-based attachment. Specifically, the coatings of the invention are highly ductile, unlike silane coatings, and thus

do not crack after manipulation such as expansion of the coated section of the device. In a method of treating a patient by implanting or otherwise providing a stent or other medical device in the patient, the amount of SOD or SODm per stent/device is about 5 to about 50 micrograms (μg). In one embodiment in which the vulnerable plaque is located on only one side of the blood vessel and is thus asymmetric or eccentric, so that the SOD or SODm coating is provided on less than the entire circumference of the stent. The eccentric SOD or SODm coating is thus oriented during implantation to be placed at the location of the eccentric vulnerable plaque.

In another embodiment, the SOD or SODm is bonded to the device in a coating comprising the coating **26** discussed above, comprising a grafting component blended with the SOD or SODm agent before being applied to the device. The discussion above relating to coating **26** applies to this embodiment of the SOD coating, except that the hydrophilic agent of the coating **26** is replaced with SOD or a SODm. In an alternative embodiment discussed below, the coating **26** may include both the hydrophilic agent and a bio-active agent such as the SOD or SODm, a nitric oxide donor, a peptide, and the like.

In another embodiment, the SOD or SODm, or other therapeutic or diagnostic agent as discussed herein, is bonded to the device by reacting a nucleophile such as a primary amine functional group on the agent with functional groups of a homomultifunctional oligomer, by a reaction mechanism known as Michael Addition. A base coat comprising a homomultifunctional oligomer such as urethane acrylate oligomer and photoinitiator(s), applied to a medical device and cured, has many acrylate groups at the air interface which do not react due to the inhibitory effects of oxygen. These free, or unpolymerized, acrylate groups, comprising alpha, beta unsaturated carbonyl compounds, are available for subsequent reaction with a nucleophile such as a primary amine functional compound. The curing of the oligomer produces further polymerization and crosslinking and the base coat adheres to a metal or polymeric medical device. A top coat can then be applied to the base coat, so that the amine functional group of the top coat agent bonds to the free acrylate groups of the base coat. The resulting coating is similar to coating **19**, except that separate grafting and binding compounds are not required in the base coat, due to the presence of the homomultifunctional compound with free acrylate groups for bonding the top coat compound. The top coat compound preferably has a strong nucleophile such as a primary amine. In a presently preferred embodiment, the homomultifunctional oligomer is urethane acrylate, however a variety of suitable compounds can be used including epoxy acrylates. Specifically, for example, a base coat solution comprising 2.0 grams of urethane acrylate (12-829 available from Henkel), 15 grams ethyl acetate, 3 grams n-butyl acetate, 0.08 grams benzophenone, 0.08 grams hydroxycyclohexyl phenyl ketone, and 0.2 grams cellulose acetate butyrate is applied by dip or spray coating a stainless steel stent and cured in front of a medium pressure mercury bulb for about 5 minutes to form a durable base coat. The base coated stent is immersed for about 18 hours at 55° C. in a 0.5 mg/ml solution of the top coat agent such as SODm (Metaphore Pharmaceuticals RM35-4) containing a primary amine ligand, to bond the top coat to the base coat. Alternatively, a spacer such as a PEG spacer, and specifically an omega-amino-alpha-carboxyl PEG can be used to bond the top coat compound to the base coat free acrylate groups. Thus, the PEG is first bonded to the base coat by dipping the device having the cured base coat thereon in a solution of the PEG to couple the PEG amino terminus to the acrylate groups. The device is rinsed and then exposed to the top coat agent, as for example, by immersion in a solution of a linker such as 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and SODm. EDC effects an imide linkage between the PEG carboxyls and the primary amine of the SODm, so that the SODm is bonded to a PEG which is bonded to the base coat. Alternatively, the top coat solution can be a mixture of the agent (e.g., SODm) and a mono primary amine terminated PEG, so that exposing the base coat to the top coat solution produces top coat comprising a mixed population of SODm and PEG, giving the benefits of both species, i.e., catalytic elimination of superoxide and a non-fouling surface.

Similarly, in another embodiment, the agent is blended or mixed with a homomultifunctional compound to form a solution before being applied to the device. The homomultifunctional compound has unsaturated acrylate groups which react with strong nucleophiles such as amines by the Michael Addition reaction mechanism discussed above. Thus, in the single layer coating, some proportion of the acrylate groups can be reacted with an amine functional group of an agent of interest such as a SODm having a amine pendant ligand, to effect covalent attachment of the SODm to the device. Sufficient acrylate groups must remain to provide adequate polymerization during curing of the coating, as by exposure to ultraviolet radiation. In a presently preferred embodiment, the homomultifunctional compound mixed with the agent of interest comprises trimethylolpropane triacrylate, although other compounds can be used including a urethane acrylate and any acrylate provided the compound is soluble in the solvent system (e.g., a water soluble acrylate). A variety of suitable agents can be bonded to the free acrylate groups of the homomultifunctional compound, as discussed herein, including SOD and SODm, amine functional nitric oxide (NO) donors such as Spermine diazeniumdiolate, and peptides with terminal Lysine or Arginine units. In one embodiment, a compound such as polyethylene oxide (PEO) is also included in the solution containing the homomultifunctional agent and the agent of interest such as a SODm, to provide both lubricity and anti-fouling for the SODm coating. Specifically, for example, a solution of 673 grams of 2-propanol, 0.4 to 4.5 grams, preferably 1.2 grams of trimethylolpropane triacrylate, 0.018 grams benzophenone, 0.018 grams hydroxycyclohexyl phenyl ketone, 7.5 grams polyethylene oxide (PEO) (1 M Daltons), 116 grams water, 0.01 to 1.2 grams, preferably 0.4 grams M040470 SODm available from Metaphor Pharmaceuticals, and 0.375 grams KBr is applied to a medical device and cured, to form a coating thereon. The resulting coating therefore comprises an embodiment of coating **26** discussed above, in which the coating **26** includes both the hydrophilic agent and a bio-active agent such as the SODm Thus, the KBr provides the crosslinked network with uncrosslinked domains previously discussed above in relation to coating **26**. Additionally, the KBr affects PEO morphology resulting in improved resistance to particle shedding from the coated device. Similarly, the bio-active agent can be omitted from the coating **26**, and a hydrophilic compound such as polyethylene amine can be used to provide a lubricious coating **26**. Thus, unlike PEO which does not have the required nucleophile, polyethylene amine has amine groups which bond to the free acrylate groups of the homomultifunctional compound.

In a presently preferred embodiment, the SOD or SODm coating is applied to a stent or stent cover for implanting in

a patient's blood vessel. However, the SOD or SODm coating can be applied to a variety of devices, such as pacemaker leads, catheters including balloon catheters, and vascular grafts. When the SOD or SODm coating comprising coating **19** having a base and top coat, is applied to a metal stent, preferably a primer coating is not provided on a surface of the stent. However, in an alternative embodiment, a primer coating is provided on the surface of the stent before the base coat is applied. When the SOD or SODm coating comprising coating **26** is applied to a metal stent, preferably a primer coating is provided on a surface of the stent. A variety of suitable primers can be used as discussed above, including vinyl, acrylate, and allyl compounds.

In one embodiment of the invention, release of the therapeutic or diagnostic agent within the patient from the medical device surface is provided by the coating of the invention. Such release of the therapeutic agent from the device surface may be desirable as when the agent is effective when taken up by cells within the patient over a desired period of time. For example, an antisense oligonucleotide may be bound to the base coat by binding the antisense oligonucleotide to a sense oligonucleotide via Watson-Crick base-pairing. However, when the complemenarity of the sense sequence is varied, the dissociation constant of the base-pair bond may be controlled, to thereby control the release of the antisense oligonucleotide from the device surface. Similarly, the avidin or biotin moiety of an avidin-biotin linking agent may be chemically altered to decrease the binding constant and thereby tailor the in vivo half life of the avidin-biotin complex. Additionally, linking agents such as liposomes and microsponges can be acted upon, as by application of mechanical or thermal stress, to cause them to release the therapeutic agents contained thereby. Microcapsules, such as microsponges bound to the surface of a medical device may be exposed to ultrasound which results in release of the therapeutic agent contained within the pores of the microsponges. In the case of a stent or other implanted medical device, the ultrasound may be applied noninvasively upon a return trip to the doctor so that the release of the therapeutic agent from the stent may occur at a desired time, which may be days, weeks, or months after the coated stent is implanted in the patient.

As discussed above, a variety of suitable therapeutic, diagnostic or hydrophilic agents may be used, and in some embodiments, a linking agent may be used to bind the therapeutic, diagnostic, or hydrophilic agent to the base coat. The use of a linking agent and the type of linking agent used depends on the nature of the therapeutic, diagnostic or hydrophilic agent. Those therapeutic agents which have the functional groups outlined above may be directly attached to the surface and/or may be attached by a linking agent. For example, proteins, peptides, antisense oligonucleotides, extracellular matrix proteins, and nitric oxide donating compounds have amine groups and hydroxyl functional groups which bind to isocyanate or aldehyde of the binding component, to bind the agent directly to base coat. Linking agents such as microsponges, liposomes and biotin-avidin complexes must be used for binding the agents which do not have the functional groups, and they may be used for binding the agents which do have the required functional groups. For example, any of the above listed therapeutic agents in addition to VEGF, Taxol, Paclitaxel, Carboplatin, and Cisplaten may be contained in a liposome or microsponge linking agent. Similarly, peptides, proteins, antibodies, and oligonucleotides have amine and carboxyl functional groups which bind to biotin of an avidin-biotin linking agent.

The presently preferred method of coating the device with the coating(s) is by dip coating at a given rate. However, the device may be coated by numerous suitable methods, including but not limited to, spray coating, wipe coating, or other techniques known in the art. Many suitable solvents may be used in the coating solutions including but not limited to water, alcohols, and ketones.

In the presently preferred embodiments, the device is a polymeric catheter, or a metal guidewire coated with a primer or without a primer, having a hydrophilic coating of the invention, or the device is a metal device such as a stent coated with a therapeutic or diagnostic coating of the invention. However, the device can be any intracorporeal medical device in which modification of surface properties, such as by addition of a therapeutic or diagnostic agent, or by a reduction of friction or modification of the surface absorption properties, is desired. The surface of the device is generally cleaned before coating with the primer or the hydrophilic coating solutions, and may optionally be plasma treated to improve coating adhesion.

The therapeutic, diagnostic, or hydrophilic coating may be applied to all or part of the medical device. In the embodiments illustrated in FIGS. **1** and **5**, the coating is on both the catheter shaft and the catheter balloon. In a presently preferred embodiment of the hydrophilic coating of the invention, the lubricious hydrophilic coating **18**, **26** on a dilatation catheter covers the outer surfaces of both the catheter shaft and balloon, as illustrated in FIGS. **1** and **5**. However, the hydrophilic coating may be applied to various catheter surfaces, including an inner surface of the catheter to facilitate displacement of objects, such as a guidewire, within a lumen of the catheter, or an outer surface of the inner tubular member **22**. Also, the hydrophilic coating **18**, **26**, **27** may be applied to less than the entire outer surface of the device, as when a proximal portion of the catheter or guidewire is left uncoated to provide a handling location, or when the balloon is left uncoated to provide frictional engagement with the patient when the balloon is inflated. For example, in a typical balloon angioplasty catheter of 144 cm, the coating **18**, **26** would be applied to about 2 cm to about 105 cm of the catheter. When the device is a guidewire, the coating **27** would be applied to about 2 cm to about 40 cm of the total guidewire length of 175 cm.

The following examples more specifically illustrate the invention. The percent values for the coating components is a percent by weight of the total formula weight.

EXAMPLE 1

Formula for Therappeutic, Diagnostic, or Hydrophylic Coatings Having a Base Coat and a Top Coat

Coating Layer	Component	% of Non-Votatile	% of Total Formula
Therapeutic, Diagnostic, or Hydrophilic Coating Formula I:			
Base coat	1. Binding component: polyaziridine or polycarbodiimide compound	5–70%	
	2. Grafting component: vinyl or acrylic functional monomer/oligomer	10–95%	
	3. Photoinitiators	0.05–10%	
	4. Solvents	N/A	40–99%

-continued

Coating Layer	Component	% of Non-Votatile	% of Total Formula
Top coat	1. Therapeutic, diagnostic, or hydrophilic agent: carboxyl containing compound		0.05–15%
	2. Solvents		84–99.5%
	3. Amine or base		0–5%
Therapeutic, Diagnostic, or Hydrophilic Coating Formula II:			
Base coat	1. Binding component: Isocyanate functional monomer/oligomer/polymer	5–90%	
	2. Grafting component: vinyl or acylic functional monomer/oligomer	5–95%	
	3. Isocyanate catalyst	0–2%	
	4. Photoinitiators	0.05–10%	
	5. Solvents	N/A	40–99%
Top coat	1. Therapeutic, diagnostic, or hydrophilic agent: hydroxy or amine containing compound.		0.05–20%
	2. Solvents		80–99.5%
Therapeutic, Diagnostic, or Hydrophilic Coating Formula III:			
Base coat	1. Binding component: aldehyde compound	5–90%	
	2. Grafting component: vinyl or acrylic functional monomer/oligomer	5–90%	
	3. Photoinitiators	0–10%	
	4. Solvents	N/A	40–99%
Top coat	1. Therapeutic, diagnostic, or hydrophilic agent: amine containing compound.		0.01–20%
	2. Solvents		80–99.9%

EXAMPLE 2

Device Coated with a Base Coat and a Hydrophilic Top Coat of Formula I

A base coat comprising 0.5 grams (gm) tri-aziridine oligomer (Zeneca cx-100), 1.5 gm trimethylol propane tri-acrylate, with an intermediate chain extension of 200 molecular weight (mol. wgt.) PEG (Henkel Photomer 4158), 0.004 gm benzophenone and 0.004 gm. 2,2 dimethoxy-2-phenylacetophenone, in 17.9 gm n-butyl acetate was applied to a coronary dilatation catheter that had been chemically cleaned and plasma treated by dip coating the catheter in a base coat solution at 20 inches per minute. The base coated device was dried for 20 seconds at 110° F., then irradiated in front of a Fusion Systems, "H" Bulb, ultra-violet source for 20 seconds at a minimum intensity of 50 milliwatts per square centimeter. A top coat of 1.5 gm poly(acrylic acid) (mol. wgt. 250K), 99 gm water, 25 gm 2-propanol, and 0.5 gm 28% NH_3 to increase acrylic acid solubility, was then applied by dip coating the base coated device in a top coat solution at 20 inches per minute. The coated device was then dried in a convection oven at 55° C. for 15 minutes. The dried coated device was then dipped in 0.1 N KOH, and rinsed freely with water, to neutralize any free carboxyl groups on the hydrophilic polymer to increase the hydrophilic character of the topcoat and enhance its lubricity. The resulting catheter having a lubricious hydrophilic coating is extremely lubricious when wet, and the coating showed resistance to wearing off. If rubbed repeatedly under running water and then tested for lubricity against an excised porcine aorta counter surface, the catheter had a coefficient of friction of 0.08. A similar unit without the basecoat of the invention had a coefficient of friction of 0.32, which is equivalent to an uncoated catheter.

EXAMPLE 3

Device Coated with a Base Coat and a Hydrophilic Top Coat of Formula II/III

The procedure outlined above in Example 2 was performed using lubricious hydrophilic coatings from the class of coatings labeled "Formula II" and "Formula III" in Example 1, except that the dried coated device is not dipped in a basic neutralizing solution. Thus, the base coat was applied to a coronary dilatation catheter that was chemically cleaned and plasma treated, by dip coating at 20 inches/min. The base coated catheter was then dried for 20 seconds at 110° F., and then irradiated in front of an ultra-violet source (Fusion Systems, "H" Bulb) for 20–90 sec. at a minimum intensity of 50 milliwatts per square centimeter. The top coat was then applied by dip coating at 20 in./min., and the coated catheter was baked in a convection oven at 55° C. for 15 min. The resulting catheter having a lubricious hydrophilic coating is extremely lubricious when wet, and the coating showed resistance to wearing off.

The specific coatings used were as follows:

For Formula II, the base coat was 1.5 gm isocyanurate trimer of 1,6 hexamethylene diisocyanate (Bayer Desmodur N-3300), 0.5 gm trimethylol propane tri-acrylate, with an intermediate chain extension of 200 mol. wgt. PEG (Henkel Photomer 4158), 0.004 gm benzophenone, 0.004 gm 2,2 dimethoxy-2-phenylacetophenone, 0.0005 gm dibutyl tin dilaurate, and 17.9 gm n-butyl acetate, and the top coat was 2.0 gm poly(vinyl alcohol) (mol. wgt. 100K), and 98.0 gm water.

For Formula III, the base coat was 2.0 gm of glutaraldehyde (25% in water), 1.5 gm trimethylol propane tri-acrylate, with an intermediate chain extension of 200 mol. wgt. PEG (Henkel Photomer 4158), 0.004 gm benzophenone, 0.004 gm 2,2 dimethoxy-2-phenylacetophenone, and 17.9 gm 2-propanol, and the top coat was 2.0 gm gelatin (175 bloom, swine skin, Aldrich Chemical Co.), and 98.0 gm water.

EXAMPLE 4

Device Coated with a Base Coat and a Therapeutic or Diagnostic Top Coat of Formula II/III

A base coat comprising 12.25 grams (gm) difunctional urethane-acrylate (Henkel 12-892), 1.0 gm hydroxycyclohexylphenyl ketone (Aldrich), 1.0 gm benzophenone (Aldrich), 2.45 gm cellulose acetate butyrate (Acros), 180 gm ethyl acetate (Aldrich), and either 12.25 gm cinnamaldehyde (Aldrich) (Formula III) or 12.25 gm a,a-Dimethyl meta-isopropenyl benzyl isocyanate (i.e., TMXDI) (Cytec) (Formula II), was applied to a stent that had been sonicated in a clean IPA for 1 minute, by dip coating. The stent was extracted form the base coat solution at a rate of 10 inches per minute, and was irradiated in front of a medium pressure Mercury lamp at an intensity of 10–15 milliwatts per square centimeter, for 8 minutes. A top coat of 1.0% peptide, such as albumin, solution was then applied by immersion of the based coated stent in a top coat solution for 2 hours at 50° C. The coated stent was then removed and baked for 10 minutes at 50° C. The dried, coated stent was then soaked in distilled water for 20 minutes at 50° C., and baked until dry.

EXAMPLE 5

Formula for Lubricious Hydrophilic Coating Having a Blend of a Grafting Component and a Hydrophilic Top Coat

Component		% of Non-Volatile	% of Total Formula
1.	Grafting component: vinyl or acylic functional monomer/ oligomer	5–45%	
2.	Hydrophilic compound	50–95%	
3.	Salt	0.1–40%	
4.	Photoinitiators	0.0–10%	
5.	Solvents	N/A	80–99.9%

1.36 gm of trimethylol propane triacrylate with an intermediate chain extension of 200 mol. wgt. PEG(Henkel Photomer 4158), 0.018 gm benzophenone and 0.018 gm 2,2 dimethoxy-2-phenylacetophenone were dissolved in 30 gms 2-propanol. The solution was then added to 653 gm 2-propanol in a container equipped with a stirrer. With agitation, 7.5 gms poly(ethylene oxide), 1 million mol. wgt, was added. 1.5 gms potassium bromide was dissolved in 116 gms water, and added to above. This solution was stirred until poly(ethylene oxide) was fully dissolved, about 1 hour.

The coating was applied to a coronary dilatation catheter that was chemically cleaned and plasma treated, by dip coating at 20 in./min. The coated catheter was dried for 20 sec. at 110° F., and then UV irradiate as outlined above. When evaluated in a friction test using excised porcine aorta as a countersurface, the hydrophilic coating yields an average force of 31 gm, as opposed to 98 gm for a control silicone coating, for a 68% reduction in force.

EXAMPLE 6

Formula for Primer Coating Lubricious Hydrophilic Coatings for Coating A Metal Device

Coating Layer	Component		% of Non-Votatile	% of Total Formula
Primer coat	1.	Vinyl or acrylate containing monomer or oligomer	90–100%	
	2.	Photoinitiators	0–10%	
	3.	Solvents	N/A	60–99%
Hydrophilic coating blend	1.	Grafting component: vinyl or acrylic functional monomer/ oligomer	5–49%	
	2.	Hydrophilic compound	50–95%	
	3.	Salt	0.1–40%	
	4.	Photoinitiators	0.0–10%	
	5.	Solvents	N/A	80–99.5%

In 100 gm of ethyl acetate, was dissolved 0.05 gm benzophenone, 0.05 gm 2,2 dimethoxy-2-phenylacetophenone, and 20 gm bisphenol A ethoxylate diacrylate (Henkel Photomer 4028). The primer was applied to a chemically cleaned guidewire by dip coating at 20 in/min, and dried for 15 sec. at 100° F., and irradiated with UV source (Fusion Systems, "H", Bulb) for 25 sec. at minimum intensity of 50 milliwatts/cm^2. For the hydrophilic coating, 0.84 gm trimethylol propane triacrylate, 0.018 gm benzophenone and 0.018 gm 2,2 dimethoxy-2-phenylacetophenone was dissolved in 30 gms 2-propanol. It was added to 650 gm 2-propanol in a container equipped with a stirrer. With agitation, 7.5 gms poly(ethylene oxide), 1 million mol. wgt, was added. 0.4 gm potassium bromide was dissolved in 116 gms water and added to above. The mixture was stirred until poly(ethylene oxide) was fully dissolved, about 1 hour. The top coat was applied to the primed guidewire by dipping, drying, and then irradiating as outlined for the primer coat.

The guidewire thus coated has a durable lubricious coating when wet, resulting in a coefficient of friction of 0.03, compared to a coefficient of friction of 0.18 for a silicone coating. The hydrophilic coating was found to slough off rapidly when wet if the primer coat was omitted.

EXAMPLE 7

Device with a Base Coat and a SOD or SODm Top Coat

A base coat comprising 1.0 grams (gm) trifunctional urethane-acrylate (Henkel 12-892)(grafting component), 0.08 gm benzophenone (photoinitiator), 0.2 gm cellulose acetate butyrate (rheology modifier, i.e., viscosifier), 15 gm ethyl acetate and 3 gm n-butyl acetate (solvents), 0.08 gm hydroxycyclohexyl phenyl ketone (polymerization initiator), and 1.0 gm of either cinnamaldehyde or dimethyl meta-isopropenyl benzyl isocyanate or acetoacetoxy ethyl-methacrylate (binding component), can be applied to a stent by dip or spray coating, and cured by irradiating with medium pressure Mercury lamp for about 5 to about 8 minutes to form a base coat. A top coat solution of 0.5% SODm, such as RM 35-4 Manganese based SODm available from Metaphore Pharmaceuticals and containing a primary amine ligand, is then applied by immersion of the base coated stent in the top coat solution for 18 hours at 55° C., pH 8.5. The coated stent can then be dried. The coated stent can be rinsed repeatedly and when the surface coating is acid digested and evaluated for manganese by ICP, shows significant coupling of the SODm, or about 20 micrograms SODm per stent in the cinnamaldehyde based coating, and about 10 micrograms SODm per stent for the isocyanate based coating.

Similarly, a silicone covered pacemaker lead, sonicated in isopropyl alcohol (IPA) for 1 minute and plasma treated at 200 W for 3 minutes, is wipe coated with the base coat, and cured and coupled with SODm as described above in Example 7.

Although the invention has been described herein in terms of certain preferred embodiments, modifications and improvements thereof may be made without departing from the scope of the invention.

What is claimed is:

1. An intracorporeal medical device having a coating, the coating comprising:

a) a polymerized base coat on the device, comprising:

a binding component having at least a first functional group selected from the group consisting of isocyanate, aldehyde, oxirane, succinimide, maleimide, acetoacetoxy, aziridine, and carbodiimide; and

a grafting component selected from the group consisting of vinyl, acrylate and allyl compounds, adhered to the device and bonded to the binding component; and

b) a top coat on the base coat, comprising an agent selected from the group consisting of superoxide dis-

mutase and a superoxide dismutase mimic, or a complex of the agent and a linking agent, the agent or the linking agent having a functional group which bonds with the binding component.

2. The coated device of claim **1** wherein the superoxide dismutase mimic comprises a manganese complex of a macrocyclic polyamine ring.

3. The coated device of claim **1** wherein the top coat agent functional group comprises a pendant ligand on the superoxide dismutase or superoxide dismutase mimic.

4. The coated device of claim **3** wherein the functional group of the pendant ligand is a primary amine.

5. The coated device of claim **1** wherein the top coat agent functional group is selected from the group consisting of amine, hydroxyl, and thiol, covalently bonded to the binding component.

6. The coated device of claim **5** wherein the binding component is selected from the group consisting of aldehyde, isocyanate, oxirane, and N-hydroxy succinimide compounds when the top coat agent or linking agent functional group is an amine group.

7. The coated device of claim **5** wherein the binding component is an isocyanate compound when the top coat agent or linking agent functional group is a hydroxyl group.

8. The coated device of claim **5** wherein the binding component is an maleimide compound when the top coat agent or linking agent functional group is a thiol group.

9. The coated device of claim **1** wherein the linking agent comprises an avidin-biotin complex having an avidin moiety bound to a biotin moiety, wherein the avidin-biotin complex is bound to the binding component and to the top coat agent.

10. The coated device of claim **1** wherein the linking agent comprises a liposome, microsponge, or microsphere containing the top coat agent.

11. The coated device of claim **1** wherein the device is a catheter.

12. The coated device of claim **1** wherein the device has a metal surface with the coating thereon.

13. The coated device of claim **12** wherein the device is selected from the group consisting of stents, guidewires, and cardiac pacing leads.

14. The coated device of claim **12** wherein the device surface has a polymeric primer coating selected from the group consisting of vinyl, acrylate and allyl compounds.

15. The coated device of claim **1** having about 5 to about 50 micrograms of a superoxide dismutase mimic.

16. A method of coating an intracorporeal medical device, comprising:

a) applying to the medical device a grafting component and a binding component, wherein the grafting component is selected from the group consisting of vinyl, acrylate and allyl compounds, and the binding component has at least a first functional group selected from the group consisting of isocyanate, aldehyde, oxirane, succinimide, maleimide, acetoacetoxy, aziridine, carboxy, and carbodiimide;

b) polymerizing the grafting component, so that the grafting component adheres to the device and bonds the binding component thereto, to form a base coat on the device; and

c) applying to the base coat a top coat having an agent selected from the group consisting of superoxide dismutase and a superoxide dismutase mimic, to covalently bond the agent to the binding component.

17. The method of claim **16** wherein polymerizing the grafting component comprises irradiating the grafting component with radiation.

18. A method of treating a patient, comprising introducing into the patient a medical device having a coating on at least a section of the device, the coating comprising

a) a polymerized base coat on the device, comprising:

a binding component having at least a first functional group selected from the group consisting of isocyanate, aldehyde, oxirane, succinimide, maleimide, acetoacetoxy, aziridine, and carbodiimide; and

a grafting component selected from the group consisting of vinyl, acrylate and allyl compounds, adhered to the device and bonded to the binding component; and

b) a top coat on the base coat, comprising an agent selected from the group consisting of superoxide dismutase and a superoxide dismutase mimic, or a complex of the agent and a linking agent, the agent or the linking agent having a functional group which bonds with the binding component.

19. The method of claim **18** wherein the method comprises prevention or inhibition of restenosis at the site of a dilated lesion, and the device comprises a stent, and including implanting the stent at the site of the dilated lesion.

20. The method of claim **18** wherein the method comprises inhibition of rupture and/or erosion of vulnerable plaque, and the device comprises a stent, and including implanting the stent at the site of the vulnerable plaque.

21. The method of claim **20** wherein the vulnerable plaque is eccentric, and the top coat extends around less than an entire circumference of the stent, and implanting the stent includes orienting the stent so that the top coat is positioned at the eccentric plaque.

22. A method of providing a coating for an intracorporeal medical device, comprising:

a) applying to the medical device a solution having a grafting component and a binding component, wherein the grafting component is selected from the group consisting of vinyl, acrylate and allyl compounds, and the binding component is selected from the group consisting of polyaziridine compounds, polycarbodiimide compounds, aldehyde compounds, and isocyanate compounds;

b) polymerizing the grafting component in the presence of the binding component by irradiating the grafting component with radiation, and bonding the grafting component to the binding component, to form a base coat on the device; and

c) applying to the base coat a solution of a top coat compound comprising an agent selected from the group consisting of superoxide dismutase and a superoxide dismutase mimic, or a complex of the agent and a linking agent, the agent or the linking agent having a functional group which bonds with the binding component, so that the top coat compound bonds to the binding component, to form the coating on the medical device.

23. An intracorporeal medical device having a coating, the coating comprising:

a) a polymerized base coat on the device formed from a solution of a binding component and a grafting component polymerized and crosslinked to the binding component on the device so that the grafting component bonds to the device,

i) the binding component being selected from the group consisting of polyaziridine compounds, polycarbodiimide compounds, aldehyde compounds, and isocyanate compounds and

ii) the grafting component being selected from the group consisting of vinyl, acrylate and allyl compounds; and

b) a top coat on the base coat, comprising an agent selected from the group consisting of superoxide dismutase and a superoxide dismutase mimic, or a complex of the agent and a linking agent, the agent or the linking agent having a functional group which bonds with the binding component and which is selected from the group consisting of carboxyl groups, hydroxy groups and amine groups, bonded to the binding component.

* * * * *